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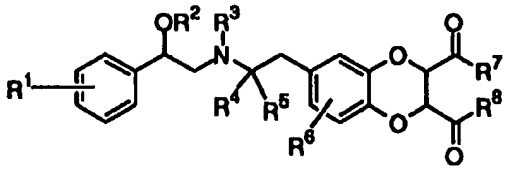
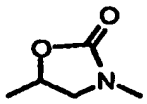


(II)



(III)

(57) Abstract

This invention relates to novel substituted 1,4-benzodioxane compounds having antidiabetic, antihyperglycemic, and antiobesity properties represented by formula (II) wherein R^1 and R^6 are independently hydrogen, C_1 to C_6 alkyl, trifluoromethyl, cyano, C_1 to C_6 alkoxy, or halogen; R^2 is hydrogen or C_1 to C_6 trialkylsilyl; R^3 is hydrogen or C_1 to C_6 alkoxycarbonyl; or R^2 and R^3 are joined to form the oxazolidinone ring (III); R^4 and R^5 are independently hydrogen or C_1 to C_6 alkyl; R^7 and R^8 are independently OR^9 or $NR^{10}R^{11}$; R^9 is hydrogen, C_1 to C_{12} alkyl, C_1 to C_{12} cycloalkyl, C_1 to C_{12} silylalkyl, phenyl, naphthyl, phenyl C^1 to C^6 alkyl, C_1 to C_6 alkoxy C_1 to C_6 alkyl, pyridyl, thiophenyl, furanyl, imidazolyl, oxazolyl, $-CHR^{12}COOR^{13}$, $-CHR^{12}C(O)R^{13}$, $-CHR^{12}CONR^{10}R^{11}$, $-CHR^{12}OCOOR^{13}$, or $-CHR^{12}OC(O)R^{13}$; R^{10} and R^{11} are independently hydrogen, C_1 to C_{12} alkyl, phenyl, naphthyl, phenyl-C_1 to C_6 alkyl, furanylalkyl, or alkoxycarbonylalkyl; R^{12} and R^{13} are independently hydrogen, C_1 to C_{12} alkyl, phenyl, naphthyl, or phenyl-C_1 to C_6 alkyl; and the pharmaceutically acceptable salts thereof, a salt thereof; an enantiomer thereof, the racemic mixtures thereof, and the diastereomeric mixtures thereof.

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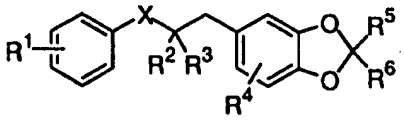
SUBSTITUTED BENZO[1,4]DIOXANES AS ANTIOBESITY AGENTS

This invention relates to novel substituted 1,4-benzodioxane compounds which have antidiabetic, antihyperglycemic, and antiobesity properties. The present invention also relates to pharmaceutical compositions comprising these compounds, methods for the preparation of these compounds, and methods for the use of these compounds in treating diabetes and/or hyperglycemia and/or obesity in mammals. The antiobesity compounds may find further use in reducing the fat content in domestic edible animals.

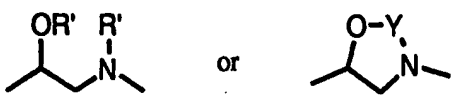
BACKGROUND OF THE INVENTION

It is well known that medicinal agents are employed in the treatment of persons suffering from diabetes, hyperglycemia, and obesity. The compounds of the present invention achieve their antidiabetic, antihyperglycemic, and antiobesity effects by acting as selective agonists at β_3 adrenergic receptors. The stimulation of these receptors on white and brown adipocytes promotes both lipolysis (breakdown of fat) and energy expenditure. Selective stimulation of β_3 adrenergic receptors is important for chronic treatment. Stimulation of other β-receptors could cause side effects such as increased heart rate (β_1 effect) and/or muscle tremor (β_2 effect). The compounds of the present invention show high selectivity for β_3 adrenergic receptors.

Bloom, et al., U.S. Patent 5,061,727, disclose substituted 5-(2-((2-aryl-2-hydroxyethyl)amino)propyl)-1,3-benzodioxoles of general formula (I)



wherein R^1 and R^4 may be one or more groups which may be the same or different and are selected from the group consisting of hydrogen, C_1 to C_4 alkyl, C_1 to C_4 alkoxy, hydroxy, halogen, trifluoromethyl, carboxy, hydroxyalkyl, alkoxycarbonyl, C_1 to C_4 thioalkyl, sulfonyl and sulfinyl; X is a divalent radical consisting of



wherein R' is selected from the group consisting of hydrogen, C_1 to C_4 alkyl and C_1 to C_4 acyl and Y is selected from the group consisting of carbonyl and thiocarbonyl; R^2 and R^3

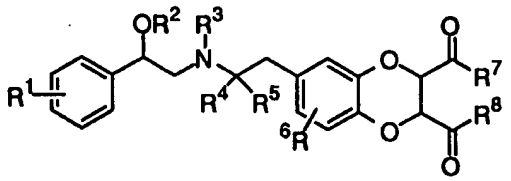
may be the same or different and are selected from the group consisting of hydrogen and C_1 to C_4 alkyl; R^5 and R^6 are selected from the group consisting of hydrogen, carboxy, alkoxycarbonyl, hydroxymethyl, $-CH_2OCH_2COOR_7$ and $-CH_2OCH_2CH_2OR_7$, where R^7 is hydrogen or C_1 to C_4 alkyl; with the provision that R^5 and R^6 may not both be hydrogen; which have antihyperglycemic and antiobesity activity.

The synthesis, antidiabetic effects, and antiobesity effects of (*R,R*)-5-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-1,3-benzodioxole-2,2-dicarboxylate, disclosed by Bloom, et al. in U.S. Patent 5,061,727, are detailed in Bloom, et al. *J. Med. Chem.*, **1992**, *35*, 3081, Largis, et al. *Drug Dev. Res.*, **1994**, *32*, 69, and Bloom, et al. *Drugs of the Future*, **1994**, *19*, 23.

The compounds of the present invention contain a 1,4-benzodioxane ring, whereas the compounds in Bloom, et al., U.S. Patent 5,061,727 contain a 1,3-benzodioxole. They retain high selectivity for the β_3 receptor and show much higher antiobesity and antihyperglycemic activity in animal models. Therefore, the compounds of this invention are useful in treating diabetes, hyperglycemia, and obesity, exhibiting minimal side effects such as heart rate increase and/or muscle tremor in humans and animals, when formulated into pharmaceutical compositions. Health-conscious individuals today are making an effort to reduce body fat through exercise and low fat diet. An invention compound can help a human reduce body fat and through treatment of domestic edible animals such as cattle, swine, sheep, goats, turkeys and chickens can provide leaner meats for human consumption.

SUMMARY OF THE INVENTION

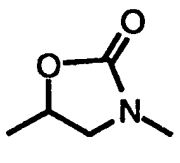
This invention provides new compounds of formula (II):



II

wherein R^1 and R^6 are independently hydrogen, C_1 to C_6 alkyl, trifluoromethyl, cyano, C_1 to C_6 alkoxy, or halogen;

R^2 is hydrogen or C_1 to C_6 trialkylsilyl; R^3 is hydrogen or C_1 to C_6 alkoxycarbonyl; or R^2 and R^3 are joined to form the oxazolidinone ring



;

R^4 and R^5 are independently hydrogen or C_1 to C_6 alkyl;

R^7 and R^8 are independently OR^9 or $NR^{10}R^{11}$;

R^9 is hydrogen, C_1 to C_{12} alkyl, C_1 to C_{12} cycloalkyl, C_1 to C_{12} silylalkyl, phenyl, naphthyl, phenyl C_1 to C_6 alkyl, C_1 to C_6 alkoxy C_1 to C_6 alkyl, pyridyl, thiophenyl, furanyl, imidazolyl, oxazolyl, $-CHR^{12}COOR^{13}$, $-CHR^{12}C(O)R^{13}$, $-CHR^{12}CONR^{10}R^{11}$, $-CHR^{12}OCOOR^{13}$, or $-CHR^{12}OC(O)R^{13}$;

R^{10} and R^{11} are independently hydrogen, C_1 to C_{12} alkyl, phenyl, naphthyl, phenyl-C_1 to C_6 alkyl, furanylalkyl, or alkoxycarbonylalkyl;

R^{12} and R^{13} are independently hydrogen, C_1 to C_{12} alkyl, phenyl, naphthyl, or phenyl-C_1 to C_6 alkyl; and the pharmaceutically acceptable salts thereof, the salts thereof;

the enantiomers thereof, the racemic mixtures thereof, and the diastereomeric mixtures thereof.

R^1 is preferably a halogen, more preferably chlorine and is preferably located at the meta-position of the benzene ring. R^2 and R^3 are each independently preferably hydrogen or are joined to form the oxazolidinone ring. R^4 and R^5 are each independently preferably hydrogen or C_1 to C_6 alkyl; more preferably hydrogen or methyl. In particularly preferred embodiments one of R^4 and R^5 is hydrogen and the other is methyl. R^6 is preferably hydrogen. R^9 is preferably hydrogen, C_1 to C_{12} alkyl, C_1 to C_{12} cycloalkyl, phenyl, phenyl C_1 to C_6 alkyl or C_1 to C_6 alkoxy C_1 to C_6 alkyl; more preferably hydrogen, methyl, ethyl, isopropyl, isobutyl, octyl, cyclopropyl, cyclohexyl, benzyl or 2-ethyloxyethyl.

When used herein, as a definition or part of a definition, the term alkyl includes both straight and branched chain alkyl groups, e.g. methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, s-butyl, pentyl and hexyl. When used herein, as a definition or part of a definition, the term halogen includes chlorine, bromine, fluorine and iodine. When used herein, as a definition or part of a definition, the term cycloalkyl includes cyclopropyl, cyclobutyl, cycopentyl and cycolohexyl.

Acid addition salts on an invention compound where a basic nitrogen is present can be prepared using a pharmaceutically acceptable inorganic or organic acid such as, but not

limited to, hydrochloric, hydrobromic, sulfuric, phosphoric, acetic, fumaric, maleic, succinic, benzoic, methanesulfonic or toluenesulfonic acid. Base addition salts can be prepared where the invention compound has a carboxylic acid group from an alkali metal oxide or hyrdoxide or alkaline earth metal oxide or hydroxide such as NaOH, KOH, $Ca(OH)_2$.

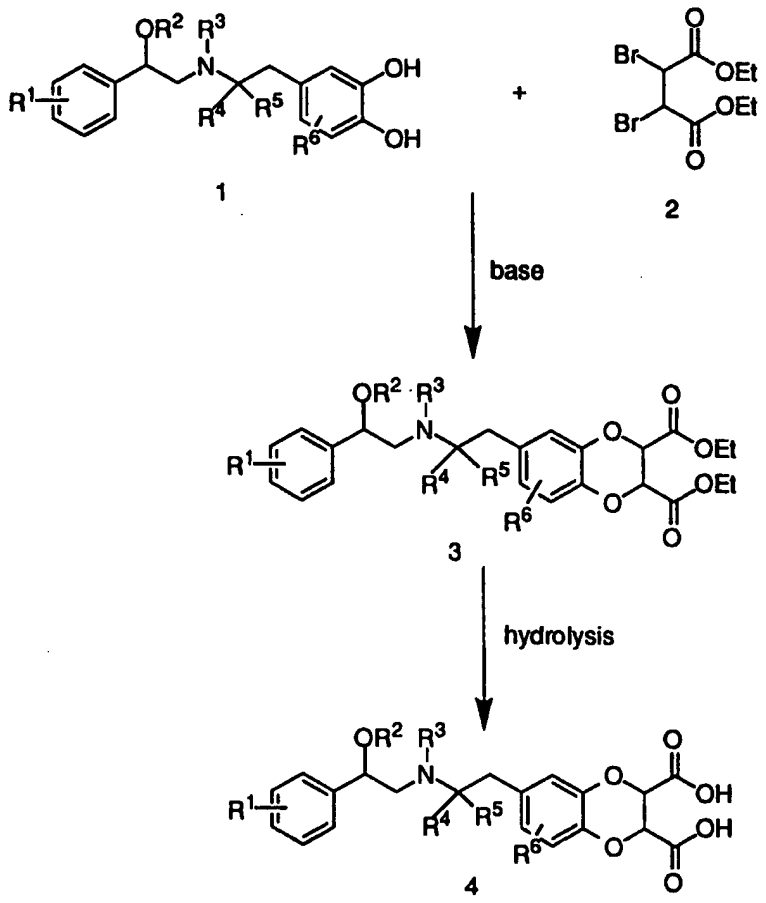
The β_3 selective compounds of this invention are useful for the treatment of non-insulin dependent diabetes mellitus, hyperglycemia and obesity in mammals. β adrenergic receptors can be divided into β_1, β_2, and β_3 subtypes. Activation of β_1 receptors invokes increase in heart rate while activation of β_2 receptors stimulates glycogen breakdown in muscle and therefore prevents glycogen synthesis. Activation of β_3 receptors stimulates lipolysis or the breakdown of brown adipose tissue triglycerides to glycerol and free fatty acids, and therby promotes the loss of fat mass. Compounds that stimulate β_3 receptors will have anti-obesity activity. Brown adipose tissue may also play a role in glucose homeostasis and β_3 adrenergic agonist may therefore also have hypoglycemic or anti-diabetic activity.

In addition to the β_3 stimulating compounds, this invention provides for a method of treating obesity, hyperglycemia, and diabetes in mammals as well as a pharmaceutical composition. In addition to treating obesity in humans for health benefit, the invention compounds may offer further health benefit in humans by use in reducing fat in meat of animals raised for human consumption such as cattle, poultry, swine, sheep and goats.

Detailed Description of the Invention

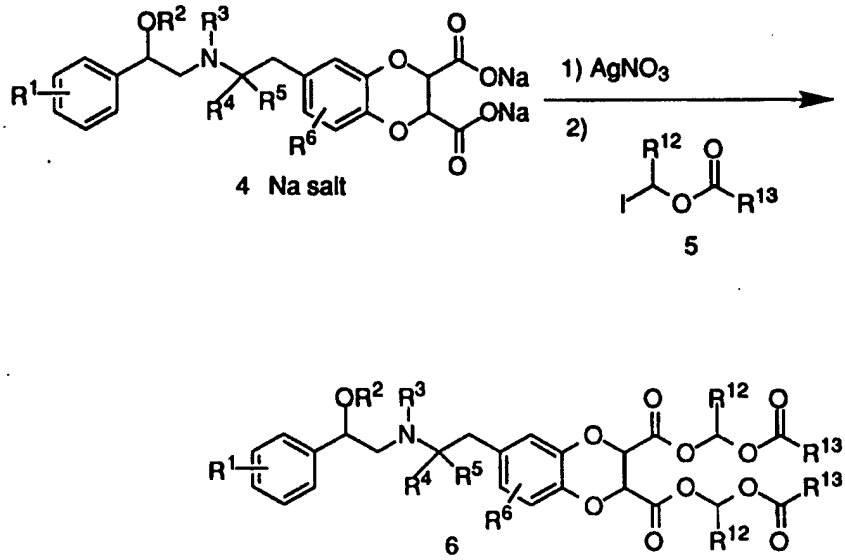
The compounds of the present invention may be prepared according to one of the general processes outlined below.

As outlined in Scheme I, a catechol 1 is treated with a base and a dibromosuccinate ester 2 to afford an oxazolidinone 3, which is hydrolyzed to yield a 1,4-benzodioxane dicarboxylic acid 4, wherein R^1, R^4, R^5, and R^6, are as defined above. Syntheses of the starting catechol 1 is described in U. S. patent 5,061,727 and U. S. patent 5,420,291.



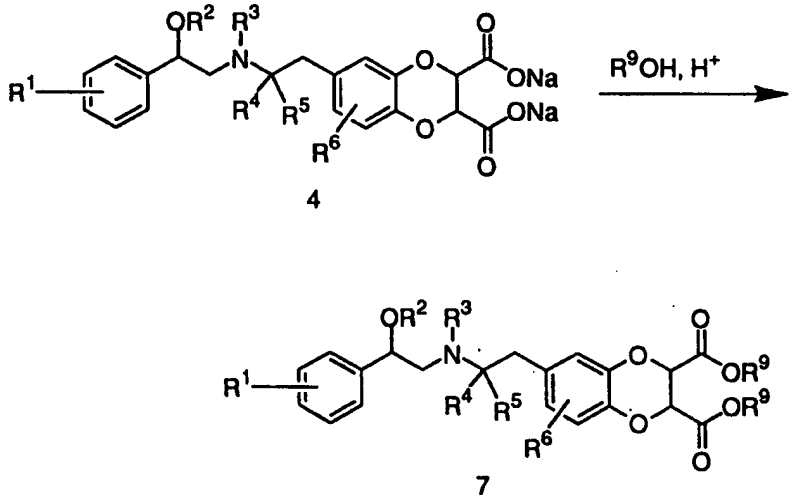
As outlined in Scheme II below, a disodium carboxylate 4 is converted to a disilver carboxylate and treated with an iodo derivative 5 to yield the diester compounds 6 wherein R^1, R^4, R^5, R^6, R^{12}, and R^{13} are as defined above.

Scheme II



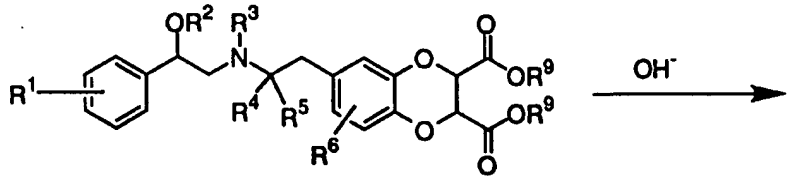
Scheme III below illustrates an alternative procedure for diester preparation wherein a dicarboxylic acid 4 is treated with an alcohol R^9OH and an acid catalyst to yield the diester compounds 7 wherein R^1, R^4, R^5, R^6, and R^9 are as defined above.

Scheme III

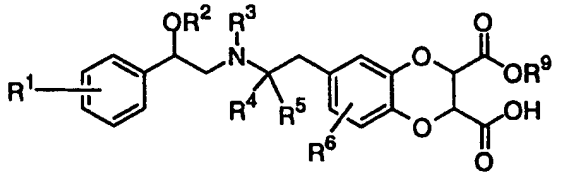


As outlined in Scheme IV below, the diester compounds 7 can be hydrolyzed under basic conditions to a monoester 8a and/or 8b, wherein R^1, R^4, R^5, R^6, and R^9 are as defined above. One or both of the regioisomers 8a and 8b may be produced in the hydrolysis reaction.

Scheme IV

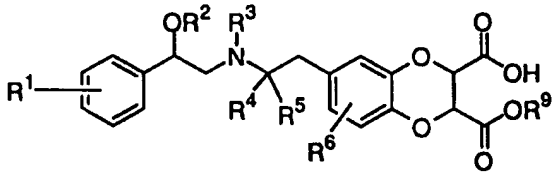


7



8a

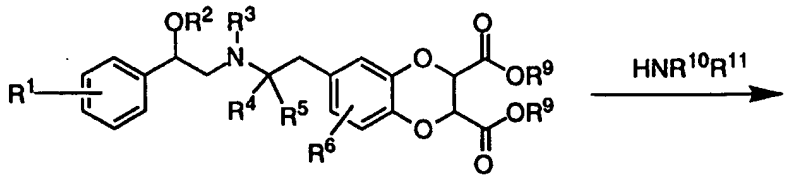
and/or



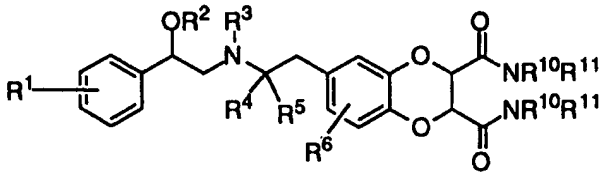
8b

As illustrated in Scheme V which follows, a diester compound 7 is reacted with an amine $HNR^{10}R^{11}$ to yield the diamide compounds 9, wherein R^1, R^4, R^5, R^6, R^9, R^{10}, and R^{11} are as defined above.

Scheme V



7



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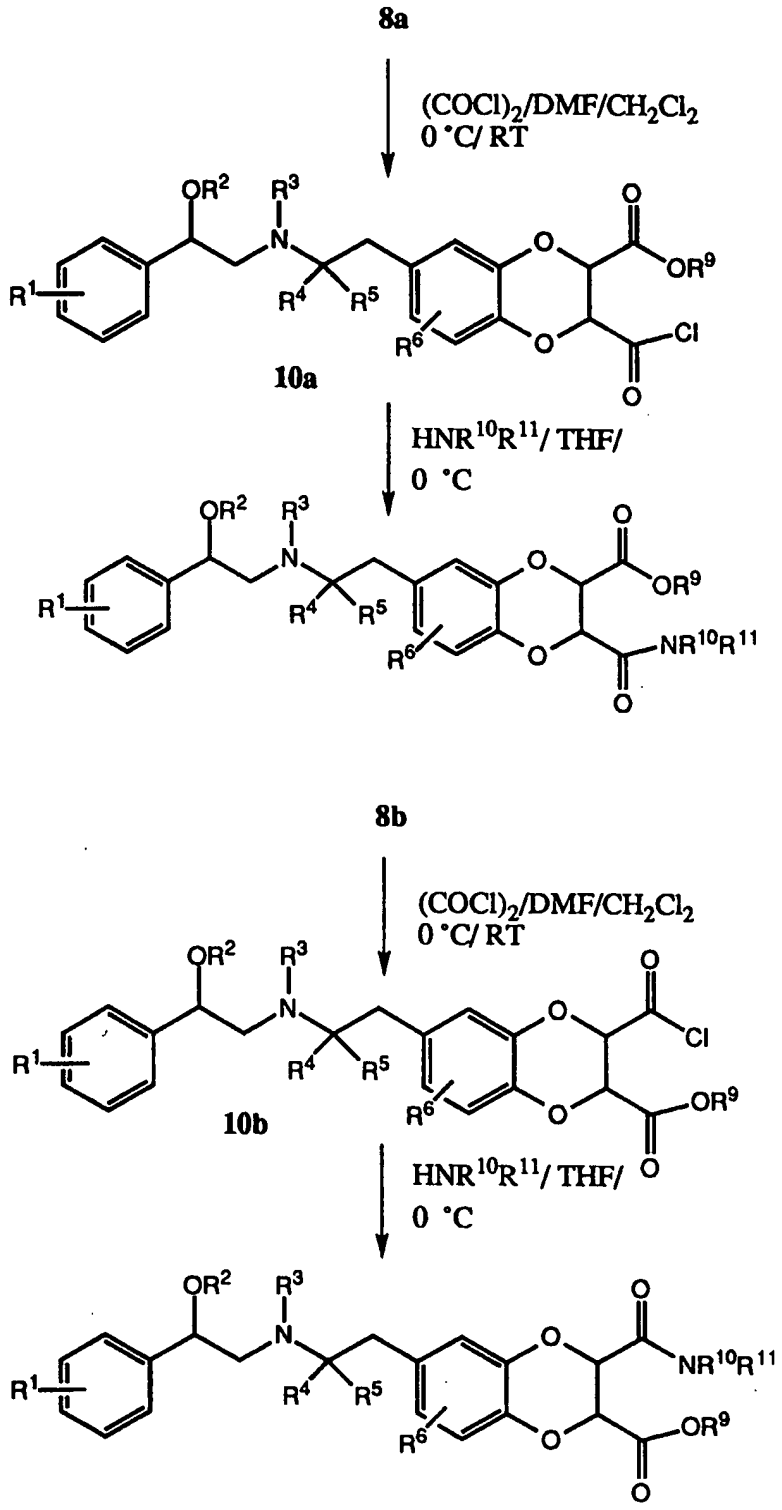
As illlustrated in Scheme VI which follows, a mono ester compound 8a or 8b may be suitably converted to a mono ester/mono acid halide derivative, e.g., the conversion to

the corresponding acid chloride may conveniently be achieved with oxalyl chloride in dimethylformamide and methylene chloride. The mono ester/mono acid halide derivative 10a or 10b may then be converted to the corresponding formula II mono ester/mono amide, e.g., by reaction with an amine of the formula $HNR^{10}R^{11}$.

Scheme VI


8a
(COCl)2/DMF/CH2Cl2
0 °C/ RT
10a
HNR10R11/ THF/
0 °C
8b
(COCl)2/DMF/CH2Cl2
0 °C/ RT
10b
HNR10R11/ THF/
0 °C

The following specific examples are included for illustration of the preparative procedures and are not to be construed as limiting to this disclosure in any way. The reagents and intermediates are either commercially available or readily prepared according to standard literature procedures by those skilled in the art of organic synthesis. Those skilled in the art may be aware of still other procedures for preparing compounds of this invention.

Example 1

6-{(2R)-2-[(5R)-5-(3-Chloro-phenyl)-2-oxo-oxazolidin-3-yl]-propyl}-2, 3-dihydro-benzo[1,4] dioxane-2,3-dicarboxylic acid dimethyl ester

A mixture of (R,R)-(±)-5-(3-chlorophenyl)-3-(2-(3,4-dihydroxyphenyl)-1-methylethyl)-2-oxazoldinone (3.47 g, 10 mmol), meso 1,2-dibromo dimethyl succinate (3,06 g, 10 mmol) and anhydrous K_2CO_3 was refluxed in acetone for six hours. The reaction mixture was then filtered and the residue was washed with acetone. The combined acetone filtrate was concentrated and the crude product obtained was purified by silica-gel column chromatography by eluting it with 3:1 hexane: ethylacetate. Pale yellow liquid. Yield 2.8 g (57%) M^+H.

Example 2

6-{2-5-(3-Chloro-phenyl)-2-oxo-oxazolidin-3-yl]-propyl}-2,3-dihydro-benzo[1,4]dioxane-2,3-dicarboxylic acid 3-methyl ester

To a stirred ethanolic solution of 6-{(2R)-2-[(5R)-5-(3-chloro-phenyl)-2-oxo-oxazolidin-3-yl]-propyl}-2, 3-dihydro-benzo[1,4] dioxane-2,3-dicarboxylic acid dimethyl ester, (2.4 g, 5 mmol) sodium hydroxide (1.0 g, 25 mmol) was added. The reaction mixture was stirred for 8 hrs at room temperature. The reaction mixture was then concentrated and dissolved in water (100 ml). Concentrated hydrochloric acid was added and the separated compound was extracted with chloroform; washed well with water, dried over anhydrous magnesium sulfate; filtered and concentrated. The product was purified by silica-gel column chromatography by eluting it with chloroform.
Yield: 2.0 g solid; mp 198°C; M^+H 476.

Example 3

(2,3-cis)-6-{(2R)-2-[(2R)-2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-propyl}-2,3-dihydro-benzo[1,4]dioxane-2,3-dicarboxylic acid

6-{(2R)-2-[(5R)-5-(3-Chloro-phenyl)-2-oxo-oxazolidin-3-yl]-propyl}-2, 3-dihydro-benzo[1,4] dioxane-2,3-dicarboxylic acid dimethyl ester, (2.4 g, 5 mmol) and sodium hydroxide (1.0 g, 25 mmol) were refluxed in ethanol: water (9:1, 50 ml) for seventy-two hours. The reaction mixture was concentrated and the residue was dissolved in water (50 ml). It was neutralized with 1N HCl and the separated solid was filtered;

washed well with water and air dried. It was found to be pure enough for further transformations.
Yield: 2.0 g; mp 220°C; M^+H 436.

Example 4

(2,3-cis)-6-{(2R)-2-[(2R)-2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-propyl-2,3-dihydro-benzo[1,4] dioxane-2,3-dicarboxylic acid diisopropyl ester

Example 5

(2,3-cis)-6-{(2R)-2-[(2R)-2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-propyl}-2,3-dihydro-benzo[1,4]dioxane-2,3-dicarboxylic acid 3-isopropyl ester

Hydrogen chloride gas was passed through isopropanol (100 ml) at 0°C for fifteen minutes and the (2,3-cis)-6-{(2R)-2-[(2R)-2-(3-chloro-phenyl)-2-hydroxy-ethylamino]-propyl}2,3-dihydro-benzo[1,4] dioxane-2,3-dicarboxylic acid (2.15 g, 5 mmol) was added. The reaction mixture was refluxed for twenty-four hours and it was concentrated. The residue obtained was neutralized with sodium bicarbonate solution and extracted with chloroform. It was dried over anhydrous sodium sulfate; filtered and concentrated. The product obtained was purified by silica-gel column chromatography by eluting it initially with chloroform and then with chloroform:methanol (9:1). The diester eluted out first and was followed by the monoester.

(2,3-cis)-6-{(2R)-2-[(2R)-2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-propyl-2,3-dihydro-benzo[1,4] dioxane-2,3-dicarboxylic acid diisopropyl ester.
Amorphous; Yield 850 mg(32%); M^+H 520.

(2,3-cis)-6-{(2R)-2-[(2R)-2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-propyl}-2,3-dihydro-benzo[1,4]dioxane-2,3-dicarboxylic acid-3-isopropyl ester.
Amorphous; Yield 700 mg (29%) M^+H 478.

General Procedure to Prepare (2,3-cis)-6-{(2R)-2-[(2R)-2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-propyl}-2, 3-dihydro-benzo[1,4]dioxane-2,3-dicarboxylic acid alkyl and cycloalkyl esters.

Hydrogen chloride gas was passed through the appropriate alcohol (100 ml) at 0°C for fifteen minutes and the (2,3-cis)-6-{(2R)-2-[(2R)-2-(3-chloro-phenyl)-2-hydroxy-ethylamino]-propyl}2,3-dihydro-benzo[1,4] dioxane-2,3-dicarboxylic acid (2.15 g, 5 mmol) was added. The reaction mixture was heated to 100°C for forty-eight hours. At the end, excess alcohol was removed under reduced pressure and the residue was neutralized with sodium bicarbonate solution. The product obtained was extracted with chloroform; washed well with water; dried over anhydrous magnesium sulfate; filtered and concentrated. The products were purified by silica-gel column chromatography. Initially the column was eluted with chloroform and later with 9:1 chloroform:methanol.

Example 6

(2,3-cis-)-6-{(2R)-2-[(2R)-2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-propyl}-2,3-dihydro-benzo[1,4]dioxane-2,3-dicarboxylic acid dibutyl ester

The title compound was prepared from (2,3-cis)-6-{(2R)-2-[(2R)-2-(3-chloro-phenyl)-2-hydroxy-ethylamino]-propyl}2,3-dihydro-benzo[1,4] dioxane-2,3-dicarboxylic acid (2.15 g, 5 mmol) and n-butanol according to the General Procedure above to yield a brown oil: 1.1 g (40%); M^+H 548.

Example 7

(2,3-cis)-6-{(2R)-2-[(2R)-2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-propyl}-2, 3-dihydro-benzo[1,4]dioxane-2,3-dicarboxylic acid bis-(2-ethoxy-ethyl) ester

The title compound was prepared from (2,3-cis)-6-{(2R)-2-[(2R)-2-(3-chloro-phenyl)-2-hydroxy-ethylamino]-propyl}2,3-dihydro-benzo[1,4] dioxane-2,3-dicarboxylic acid (2.15 g, 5 mmol) and 2-ethoxyethanol. Two diastereomers were obtained as amorphous solids: diastereomer 1: Yield 800 mg (33%) M^+H 480.
diasteromer 2: Yield 600 mg (25%) M^+H 480.

Example 8

(2,3-cis)-6-{(2R)-2-[(2R)-2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-propyl}-2,3-dihydro-benzo[1,4]dioxane-2,3-dicarboxylic acid diethyl ester

The title compound was prepared from (2,3-cis)-6-{(2R)-2-[(2R)-2-(3-chloro-phenyl)-2-hydroxy-ethylamino]-propyl}2,3-dihydro-benzo[1,4] dioxane-2,3-dicarboxylic acid (2.15 g, 5 mmol) and ethanol according to the General Procedure above to yield a brown oil: 600 mg (24%); M^+H 492.

Example 9

(2,3-cis)-6-{(2R)-2-[(2R)-2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-propyl}-2,3-dihydro-benzo[1,4]dioxane-2,3-dicarboxylic acid dicyclohexyl ester

The title compound was prepared from (2,3-cis)-6-{(2R)-2-[(2R)-2-(3-chloro-phenyl)-2-hydroxy-ethylamino]-propyl}2,3-dihydro-benzo[1,4] dioxane-2,3-dicarboxylic acid (2.15 g, 5 mmol) and cyclohexanol according to the General Procedure above to yield a brown foam: 750 mg (40%); M^+H 600.

Example 10

(2,3-cis)-6-{(2R)-2-[(2R)-2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-propyl}-2,3-dihydro-benzo[1,4]dioxane-2,3-dicarboxylic acid dicyclopentyl ester

The title compound was prepared from from (2,3-cis)-6-{(2R)-2-[(2R)-2-(3-chloro-phenyl)-2-hydroxy-ethylamino]-propyl}2,3-dihydro-benzo[1,4] dioxane-2,3-dicarboxylic acid (2.15 g, 5 mmol) and cyclopentanol according to the General Procedure above to yield an amorphous solid: 1.4g (49%); M^+ H 572.

Example 11

(2,3-cis)-6-{(2R)-2-[(2R)-2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-propyl}-2,3-dihydro-benzo[1,4]dioxane-2,3-dicarboxylic acid dioctyl ester

The title compound was prepared from from (2,3-cis)-6-{(2R)-2-[(2R)-2-(3-chloro-phenyl)-2-hydroxy-ethylamino]-propyl}2,3-dihydro-benzo[1,4] dioxane-2,3-dicarboxylic acid (2.15 g, 5 mmol) and 1-octanol according to the General Procedure above to yield a brown foam: 1.3 g (39%); M^+H 660.

Example 12

(2,3-cis)-6-{(2R)-2-[(2R)-2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-propyl}-2,3-dihydro-benzo[1,4]dioxane-2,3-dicarboxylic acid dibenzyl ester

The title compound was prepared from from (2,3-cis)-6-{(2R)-2-[(2R)-2-(3-chloro-phenyl)-2-hydroxy-ethylamino]-propyl}2,3-dihydro-benzo[1,4] dioxane-2,3-dicarboxylic acid (2.15 g, 5 mmol) and benzyl alcohol according to the General Procedure above to yield a brown oil: 1.0 g(32%); M^+H 616.

Human Beta Adrenergic Receptor Selectivity

The activity of the test compounds on human β-adrenergic receptors was determined with Chinese hamster ovary (CHO) cells transfected with human β_3, β_2, or β_1 adrenergic receptors. The preparation of these cells has been described in Emorine, L.J., Marullo, S., Briend-Sutren, M., Patey, G., Tate, K., Delavier-Klutchko, C., Strosberg, A.D. Molecular Characterization of the Human Beta 3-Adrenergic Receptor *Science* **1989**, *245*(8), 1118-1121 and in Muzzin, P., Revelli, J.-P., Kuhne, F., Gocayne, J.D., McCombie, W.R., Venter, J.C., Giacobino, J.-P., Fraser, C.M. An Adipose Tissue-Specific Beta 3-Adrenergic Receptor. Molecular Cloning and Down-Regulation in Obesity *J. Biol. Chem.* **1991**, 226, 24053-24058. Agonist activity is indicated by increased cAMP levels in the CHO cells. Selectivity of the test compounds for the β_3 receptor was assessed by comparison with results in β_2 and β_1 adrenergic receptor transfected cells.

Procedure:

1). Chinese hamster ovary (CHO) cells transfected with human β_3, β_2, or β_1 adrenergic receptors were used in the assay.

2). Cells were grown to confluent conditions in 24 well plates.

3). Drugs were dissolved in DMSO at a concentration of 10 μM.

4). Cells were incubated with drug at 10 nM concentration for 10 min at 37° C. Isoproterenol (Standard 1) was used as the standard compound and assayed at 10 μM which gives a maximal cAMP elevation in all 3 cell types.

5). Cell cAMP concentrations were assayed using a scintillation proximity assay from Amersham Corp (Chicago, IL).

6). Activities for the test compounds are expressed as a percentage of the isoproterenol response.

Effects on Free Fatty Acid Levels in Rats

Rats respond to a single oral dose of β3 agonist by increasing plasma free fatty acids (FFA) in response to β3 receptor stimulation on the plasma membrane of the fat cell. 5-{2-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-propyl}-benzo[1,3]dioxole-2,2-dicarboxylic acid diisopropyl ester (Standard 2) was used as a standard compound. All test compounds were dosed at 0.1 mg/kg and compared to the response by Standard 2.

Procedure:

1). Drugs were dissolved in DMSO at 10 mg/mL.

2). Twenty µl of the DMSO-drug solution was added to 10 mL methyl cellulose:Tween-80 (0.5%:0.1%) for a final concentration of 20 µg/mL.

3). Methyl cellulose:tween-80 drug suspension was given via gavage (1 mL/200g body weight; or 0.1 mg/kg) to rats and blood was collected 50 min later.

4). Plasma was analyzed for free fatty acids using a kit supplied by Biochemical Diagnostics Inc. (Brentwood, N.Y.).

5). Drug response was calculated from the formula below.

$$\% \text{ FFA Response} = \frac{\text{FFA (compound) - FFA vehicle}}{\text{FFA (Standard 2) - FFA vehicle}} \times 100$$

Effects on Hyperglycemia in Mice

On the morning of Day 1 (baseline), 35 mice (male, db/db (C57BL/KsJ), Jackson Laboratories, 2 to 7 months of age and 35 to 60 g) were fasted for 4 h, weighed, and a baseline blood sample was collected from the tail-tip of each mouse without anesthesia, placed directly into a fluoride-containing tube, mixed, and maintained on ice. Food was then returned to the mice. The plasma was seperated and the levels of glucose in the plasma were dertermined by an Abbot VP Analyzer. Because of the variable plasma glucose levels of the db/db mice, the 5 mice having the most extreme (i.e., highest or lowest) plasma glucose levels were excluded and the remaining 30 mice were randomly assigned into 7 groups of equivalent mean plasma glucose level (vehicle control, ciglitazone (Standard 3), and 5 test compound groups). On the afternoon of Days 1, 2, and 3 the vehicle (0.2 mL of 2% Tween 80/saline w/v) or test compounds were administered (p.o.) to the ad libitum fed mice. On the morning of Day 4, the food was removed from the cages for 3 h, a blood sample was collected, and the mice were then given the fourth administration of test compound or vehicle. Additional blood samples were collected at 2 and 4 h after test

compound administration. Plasma glucose levels were determined. To assess test compound activity, the percent change of an animal's plasma glucose level on Day 4 (mean of 2 and 4 h values) from its level before test compound administration (Day 1 baseline sample) was determined as follows:

$$\frac{\text{Mean of 2 and 4 h samples (Day 4)}}{\text{Baseline sample (Day 1)}} \times 100$$

A 50-60% reduction of plasma glucose levels in the hyperglycemic db/db mice represents a normalization of glucose levels.

Table I

Compound (Example)	$\beta 2^a$	$\beta 3^a$	Rat Free Fatty Acid[b]
4	9%	4%	32%
5	11%	50%	6%
6	16%	51%	0%
7	33%	40%	7%
8	-	-	19%
9	1%	3%	3%
10	4%	3%	20%
11	38%	97%	5%
12	11%	27%	11%

[a] Human β receptors expressed in Chinese hamster ovary cells, compounds tested at 10 nM, results expressed as % of isoproterenol activity (increase in cAMP) at 10 μM.

[b] Elevation of plasma free fatty acids in rats, compounds tested at 0.1 mg/kg, results expressed as % of 5-{2-[2-(3-chloro-phenyl)-2-hydroxy-ethylamino]-propyl}-benzo[1,3]dioxole-2,2-dicarboxylic acid diisopropyl ester response (78% increase) at 0.1 mg/kg.

Pharmaceutical Composition

Compounds of this invention may be administered neat or with a pharmaceutical carrier to a patient in need thereof. The pharmaceutical carrier may be solid or liquid.

Applicable solid carriers can include one or more substances which may also act as flavoring agents, lubricants, solubilizers, suspending agents, fillers, glidants, compression aids, binders or tablet-disintegrating agents or an encapsulating material. In powders, the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed with a carrier having the necessary compression properties n suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain up to 99% of the active ingredient. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidine, low melting waxes and ion exchange resins.

Liquid carriers may be used in preparing solutions, suspensions, emulsions, syrups and elixirs. The active ingredient of this invention can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both or pharmaceutically acceptable oils or fat. The liquid carrier can contain other suitable pharmaceutical additives such a solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers or osmo-regulators. Suitable examples of liquid carriers for oral and parenteral administration include water (particularly containing additives as above, e.g., cellulose derivatives, preferable sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols, e.g., glycols) and their derivatives, and oils (e.g., fractionated coconut oil and arachis oil). For parenteral administration the carrier can also be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are used in sterile liquid form compositions for parenteral administration.

Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by, for example, intramuscular, intraperitoneal or subcutaneous injection. Sterile solutions can also be administered intravenously. Oral administration may be either liquid or solid composition form.

The compounds of this invention may be administered rectally in the form of a conventional suppository. For administration by intranasal or intrabronchial inhalation or insufflation, the compounds of this invention may be formulated into an aqueous or partrially aqueous solution, which can then be utilized in the form of an aerosol. The compounds of this invention may also be administered transdermally through the use of a

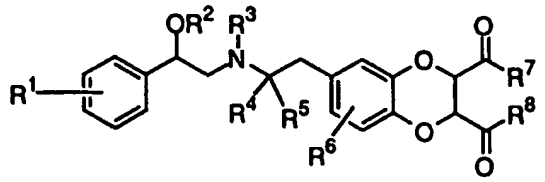
transdermal patch containing the active compound and a carrier that is inert to the active compound, is non-toxic to the skin, and allows delivery of the agent for systemic absorption into the blood stream via the skin. The carrier may take any number of forms such as creams and ointments, pastes, gels, and occlusive devices. The creams and ointments may be viscous liquid or semi-solid emulsions of either the oil in water or water in oil type. Pastes comprised of absorptive powders dispersed in petroleum or hydrophilic petroleum containing the active ingredient may also be suitable. A variety of occlusive devices may be used to release the active ingredient into the blood stream such as a semipermeable membrane covering a reservoir containing the active ingredient with or without a carrier, or a matrix containing the active ingredient. Other occlusive devices are known in the literature. Further, an invention compound may be incorporated into a controlled release subcutaneous implant for gradual release over a period of time eliminating the necessity of frequent dosing. An antiobesity invention compound may also be incorporated into animal feed for the use with livestock as a means of oral dosing.

The dosage to be used in the treatment of a specific patient suffering obesity and/or diabetes and/or hyperglycemia must be subjectively determined by the attending physician. The variables involved include the severity of the dysfunction, and the size, age, and response pattern of the patient. Treatment will generally be initiated with small dosages less than the optimum dose of the compound. Thereafter the dosage is increased until the optimum effect under the circumstances is reached. Precise dosages for oral, parenteral, nasal, or intrabronchial administration will be determined by the administering physician based on experience with the individual subject treated and standerd madical principles.

Preferably the pharmaceutical composition is in unit dosage form, e.g., as tablets or capsules. In such form, the composition is sub-divided in unit dose containing appropriate quantities of the active ingredient; the unit dosage form can be packaged compositions, for example packed powders, vials, ampoules, prefilled syringes or sachets containing liquids. The unit dosage form can be, for example, a capsule or tablet itself, or it can be the appropriate number of any such compositions in package form.

What is claimed:

1. A compound having the formula:



wherein R^1 and R^6 are independently hydrogen, C_1 to C_6 alkyl, trifluoromethyl, cyano, C_1 to C_6 alkoxy, or halogen;

R^2 is hydrogen or C_1 to C_6 trialkylsilyl; R^3 is hydrogen or C_1 to C_6 alkoxycarbonyl;

or R^2 and R^3 are joined to form the oxazolidinone ring

R^4 and R^5 are independently hydrogen or C_1 to C_6 alkyl;

R^7 and R^8 are independently OR^9 or $NR^{10}R^{11}$;

R^9 is hydrogen, C_1 to C_{12} alkyl, C_1 to C_{12} cycloalkyl, C_1 to C_{12} silylalkyl, phenyl, naphthyl, phenyl C_1 to C_6 alkyl, C_1 to C_6 alkoxy C_1 to C_6 alkyl, pyridyl, thiophenyl, furanyl, imidazolyl, oxazolyl, $-CHR^{12}COOR^{13}$, $-CHR^{12}C(O)R^{13}$, $-CHR^{12}CONR^{10}R^{11}$, $-CHR^{12}OCOOR^{13}$, or $-CHR^{12}OC(O)R^{13}$;

R^{10} and R^{11} are independently hydrogen, C_1 to C_{12} alkyl, phenyl, naphthyl, phenyl-C_1 to C_6 alkyl, furanylalkyl, or alkoxycarbonylalkyl;

R^{12} and R^{13} are independently hydrogen, C_1 to C_{12} alkyl, phenyl, naphthyl, or phenyl-C_1 to C_6 alkyl; and the pharmaceutically acceptable salts thereof,

an enantiomer or diastereomer thereof,

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 which is selected from:

6-{(2R)-2-[(5R)-5-(3-chloro-phenyl)-2-oxo-oxazolidin-3-yl]-propyl}-2, 3-dihydro-benzo[1,4] dioxane-2,3-dicarboxylic acid dimethyl ester ;

6-{2-5-(3-chloro-phenyl)-2-oxo-oxazolidin-3-yl]-propyl}-2,3-dihydro-benzo[1,4]dioxane-2,3-dicarboxylic acid 3-methyl ester;

(2,3-cis)-6-{(2R)-2-[(2R)-2-(3-chloro-phenyl)-2-hydroxy-ethylamino]-propyl}-2,3-dihydro-benzo[1,4]dioxane-2,3-dicarboxylic acid;

(2,3-cis)-6-{(2R)-2-[(2R)-2-(3-chloro-phenyl)-2-hydroxy-ethylamino]-propyl-2,3-dihydro-benzo[1,4] dioxane-2,3-dicarboxylic acid diisopropyl ester;

(2,3-cis)-6-{(2R)-2-[(2R)-2-(3-chloro-phenyl)-2-hydroxy-ethylamino]-propyl}-2, 3-dihydro-benzo[1,4]dioxane-2,3-dicarboxylic acid 3-isopropyl ester;

(2,3-cis-)-6-{(2R)-2-[(2R)-2-(3-chloro-phenyl)-2-hydroxy-ethylamino]-propyl}-2,3-dihydro-benzo[1,4]dioxane-2,3-dicarboxylic acid dibutyl ester;

(2,3-cis)-6-{(2R)-2-[(2R)-2-(3-chloro-phenyl)-2-hydroxy-ethylamino]-propyl}-2, 3-dihydro-benzo[1,4]dioxane-2,3-dicarboxylic acid bis-(2-ethoxy-ethyl) ester;

(2,3-cis)-6-{(2R)-2-[(2R)-2-(3-chloro-phenyl)-2-hydroxy-ethylamino]-propyl}-2, 3-dihydro-benzo[1,4]dioxane-2,3-dicarboxylic acid diethyl ester;

(2,3-cis)-6-{(2R)-2-[(2R)-2-(3-chloro-phenyl)-2-hydroxy-ethylamino]-propyl}-2, 3-dihydro-benzo[1,4]dioxane-2,3-dicarboxylic acid dicyclohexyl ester;

(2,3-cis)-6-{(2R)-2-[(2R)-2-(3-chloro-phenyl)-2-hydroxy-ethylamino]-propyl}-2, 3-dihydro-benzo[1,4]dioxane-2,3-dicarboxylic acid dicyclopentyl ester;

(2,3-cis)-6-{(2R)-2-[(2R)-2-(3-chloro-phenyl)-2-hydroxy-ethylamino]-propyl}-2, 3-dihydro-benzo[1,4]dioxane-2,3-dicarboxylic acid dioctyl ester;

(2,3-cis)-6-{(2R)-2-[(2R)-2-(3-chloro-phenyl)-2-hydroxy-ethylamino]-propyl}-2, 3-dihydro-benzo[1,4]dioxane-2,3-dicarboxylic acid dibenzyl ester

and pharmaceutically acceptable salts thereof.

3. A method of treating obesity in an obese mammal or a method of treating diabetes and/or hyperglycemia in a mammal having diabetes or hyperglycemia which comprises administering to said mammal a therapeutically effective amount of a compound as claimed in Claim 1 or Claim 2.

4. A method of increasing the amount of lean meat in domestic animals raised for human consumption which comprises administering to said edible animals an effective amount of a compound as claimed in Claim 1 or Claim 2.

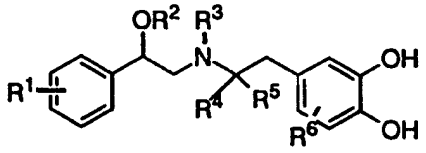
5. A pharmaceutical composition which comprises a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound as claimed in Claim 1 or Claim 2.

6. Use of a compound as claimed in Claim 1 or Claim 2 as a medicament.

7. Use of a compound as claimed in Claim 1 or Claim 2 in the preparation of a medicament for the treatment of obesity in an obese mammal or the treatment diabetes and/or hyperglycemia in a mammal having diabetes or hyperglycemia .

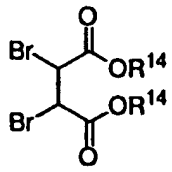
8. Process for the preparation of a compound as claimed in Claim 1 or Claim 2 which comprises:

a) reacting a catechol of formula 1



1

with a bromosuccinate ester of formula 2



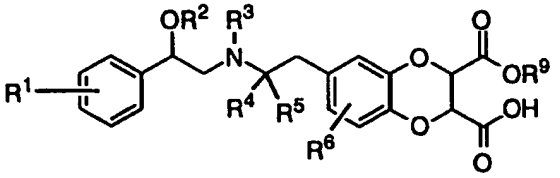
2

wherein R^{14} is C_1 to C_{12} alkyl, to provide a compound of formula II wherein R^7 and R^8 are both OR^9 and R^9 is C_1 to C_{12} alkyl;

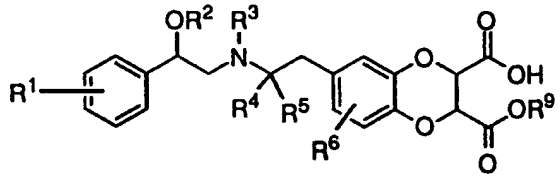
b) hydrolysing a compound of formula II, wherein R^7 and R^8 are both OR^9 and R^9 is C_1 to C_{12} alkyl, to provide a compound of formula II wherein R^7 and R^8 are both OR^9 and R^9 is hydrogen;

c) reacting the appropriate dicarboxylic acid or its salt with an alcohol of formula R^9OH, wherein R^9 is as defined in Claim 1, to provide a compound of formula II wherein R^7 and R^8 are both OR^9;

d) hydrolysing a compound of formula II wherein R^7 and R^8 are both OR^9 to provide one or both of the regioisomers 8a and 8b



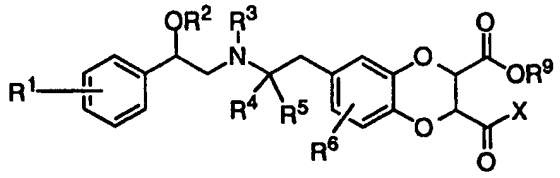
8a



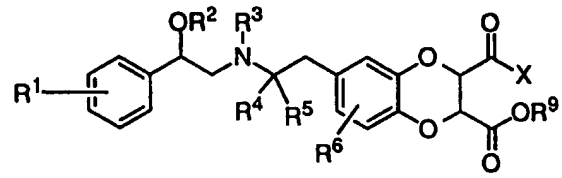
8b

e) reacting a compound of formula II wherein R^7 and R^8 are both OR^9 with an amine of formula $NR^{11}R^{12}$, wherein R^{11} and R^{12} are as defined in Claim 1, to provide a compound of formula II wherein R^7 and R^8 are both $NR^{10}R^{11}$;

or g) reacting an acid halide of the formula 10a or 10b



10a



10b

wherein X is a halogen, with an amine of the formula $HNR^{10}R^{11}$ to obtain a compound of Formula II where one of R^7 and R^8 is OR^9 and the other is $-NR^{10}R^{11}$.

INTERNATIONAL SEARCH REPORT

In' tional Application No
PCT/US 97/24019

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D319/20 C07D413/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category '	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 482 971 A (JOSEPH W. EPSTEIN ET AL.) 9 January 1996 see column 1, line 47 - column 2, line 65; claims 1-3,9,10,14-17; example 10 ---	1-8
Y	WO 96 35685 A (NISSHIN FLOUR MILLING) 14 November 1996 see claims; examples -& EP 0 825 189 A (NISSHIN FLOUR MILLING) 25 February 1998 ---	1-8
Y	US 5 061 727 A (JONATHAN D. BLOOM ET AL.) 29 October 1991 cited in the application see the whole document -----	1-8

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

' Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

3

Date of the actual completion of the international search	Date of mailing of the international search report
23 April 1998	29.04.98

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040. Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Zervas, B

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

National application No.
PCT/US 97/24019

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 4 and 6 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1 [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

ational Application No
PCT/US 97/24019

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5482971 A	09-01-96	NONE	
WO 9635685 A	14-11-96	EP 0825189 A	25-02-98
US 5061727 A	29-10-91	AU 639094 B	15-07-93
		AU 7607891 A	07-11-91
		CA 2041712 A	05-11-91
		CN 1056495 A	27-11-91
		CS 9101285 A	17-12-91
		EP 0455006 A	06-11-91
		FI 912142 A,B,	05-11-91
		HU 210596 B	29-05-95
		HU 9500457 A	30-10-95
		IL 97900 A	15-04-97
		JP 5320153 A	03-12-93
		NO 177822 B	21-08-95
		PL 165665 B	31-01-95
		PT 97540 A	31-01-92
		US 5373020 A	13-12-94
		US 5106867 A	21-04-92
		US 5151439 A	29-09-92
		US 5245053 A	14-09-93